4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-1721]

Agency Information Collection Activities; Proposed Collection; Comment Request; Investigational New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing an opportunity for public comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of 1995 (PRA), Federal Agencies are required to publish notice in the *Federal Register* concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

DATES: Submit either electronic or written comments on the collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments

until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2014-N-1721 for "Agency Information Collection Activities; Proposed Collection; Comment Request; Investigational New Drug Applications." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the

body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the *Federal Register* concerning each proposed collection of information, including each proposed extension of an existing collection of information, before

submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Investigational New Drug Application--21 CFR Part 312

OMB Control Number 0910-0014--Extension

This information collection supports FDA regulations in 21 CFR Part 312 covering Investigational New Drugs. Part 312 implements provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(i)) to issue regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

FDA is charged with implementing statutory requirements that ensure drug products marketed in the United States are shown to be safe and effective, properly manufactured, and properly labeled for their intended uses. Section 505(a) of the FD&C Act (21 U.S.C. 355(a)) provides that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless FDA has previously approved a new drug application (NDA). FDA approves an NDA only if the sponsor of the application first demonstrates that the

drug is safe and effective for the conditions prescribed, recommended, or suggested in the product's labeling. Proof must consist, in part, of adequate and well-controlled studies, including studies in humans, that are conducted by qualified experts.

The investigational new drug application (IND) regulations under 21 CFR part 312 establish reporting requirements that include an initial application as well as amendments to that application, reports on significant revisions of clinical investigation plans, and information on a drug's safety or effectiveness. In addition, the sponsor is required to give FDA an annual summary of the previous year's clinical experience. The regulations also include recordkeeping requirements pertaining to the disposition of drugs, records pertaining to individual case histories, and certain other documentation verifying the fulfillment of responsibilities by clinical investigators.

Submissions are reviewed by medical officers and other Agency scientific reviewers assigned responsibility for overseeing a specific study. The details and complexity of these requirements are dictated by the scientific procedures and human subject safeguards that must be followed in the clinical tests of investigational new drugs.

The IND information collection requirements provide the means by which FDA can monitor the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products, including the following: (1) monitor the safety of ongoing clinical investigations; (2) determine whether the clinical testing of a drug should be authorized; (3) ensure production of reliable data on the metabolism and pharmacological action of the drug in humans; (4) obtain timely information on adverse reactions to the drug; (5) obtain information on side effects associated with increasing doses; (6) obtain information on the drug's effectiveness; (7) ensure the design of well-controlled, scientifically valid studies; and (8) obtain other

information pertinent to determining whether clinical testing should be continued and information related to the protection of human subjects. Without the information provided by industry as required under the IND regulations, FDA cannot authorize or monitor the clinical investigations that must be conducted before authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to ensure the safety of subjects, to ensure that a study will be conducted ethically, and to increase the likelihood that the sponsor will conduct studies that will be useful in determining whether the drug should be marketed and available for use in medical practice.

To assist respondents with certain reporting requirements under part 312, we have developed two forms: Form FDA 1571 entitled, "Investigational New Drug Application (IND)" and Form FDA 1572 entitled, "Statement of Investigator." Anyone who intends to conduct a clinical investigation must submit Form FDA 1571 as instructed. The reporting elements include: (1) a cover sheet containing background information on the sponsor and investigator; (2) a table of contents; (3) an introductory statement and general investigational plan; (4) an investigator's brochure describing the drug substance; (5) a protocol for each planned study; (6) chemistry, manufacturing, and control information for each investigation; (7) pharmacology and toxicology information for each investigation; and (8) previous human experience with the investigational drug. Form FDA 1572 is executed and submitted by the IND sponsor before an investigator may participate in an investigation. It includes background information on the investigator as well as the investigation, and a general outline of the planned investigation and study protocol.

Below, we estimate the burden of the information collection as reported by FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) as follows:

Table 1.--Estimated Annual Reporting Burden for Human Drugs (CDER)[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
§ 312.2(e); Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.	400	1	400	24	9,600
§ 312.8; Requests to charge for an investigational drug.	74	1.23	91	48	4,368
§ 312.10; Requests to waive a requirement in part 312.	86	1.84	158	24	3,792
§ 312.23(a) through (f); IND content and format (including Form FDA 1571)	2,187	1.7	3,718	1,600	5,948,800
§ 312.30(a) through (e); Protocol amendments.	4,418	5.52	24,387	284	6,925,908
§ 312.31(b); Information amendments.	6,691	3.32	22,214	100	2,221,400
§ 312.32(c) and (d); IND safety reports.	867	15.78	13,681	32	437,792
§ 312.33(a) through (f); IND annual reports.	3,376	2.86	9,655	360	3,475,800
§ 312.38(b) and (c); Notifications of withdrawal of an IND.	930	1.61	1,497	28	41,916
§ 312.42; Sponsor requests that a clinical hold be removed, including sponsor submission of a complete response to the issues identified in the clinical hold order.	198	1.38	273	284	77,532
§ 312.44(c) and (d); Sponsor responses to FDA when IND is terminated.	12	1.16	14	16	224
§ 312.45(a) and (b); Sponsor requests for or responses to an inactive status determination of an IND by FDA.	231	1.84	425	12	5,100
§ 312.47; Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.	122	1.51	184	160	29,440
§ 312.54(a); Sponsor submissions to FDA concerning investigations involving an exception from informed consent under § 50.24.	15	2.4	36	48	1,728
§ 312.54(b); Sponsor notifications to FDA and others concerning an IRB determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in § 50.24(a).	2	1	2	48	96
§ 312.56(b), (c), and (d); Sponsor notifications to FDA and others	6,100	7	42,700	80	3,416,000

Table 1.--Estimated Annual Reporting Burden for Human Drugs (CDER)[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
resulting from: (1) the sponsor's monitoring of all clinical investigations and determining that an investigator is not in compliance with the investigation agreements; (2) the sponsor's review and evaluation of the evidence relating to the safety and effectiveness of the investigational drug; and (3) the sponsor's determination that the investigational drug presents an unreasonable and significant risk to subjects.					
§ 312.58(a); Sponsor's submissions of clinical investigation records to FDA on request during FDA inspections.	73	1	73	8	584
§ 312.70; During the disqualification process of a clinical investigator by FDA, the number of investigator responses or requests to FDA following FDA's notification to an investigator of its failure to comply with investigation requirements.	4	1	4	40	160
§ 312.110(b)(4) and (b)(5); Written certifications and written statements submitted to FDA relating to the export of an investigational drug.	11	26.28	289	75	21,675
§ 312.120(b); Submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND.	1,414	8.62	12,189	32	390,048
§ 312.120(c); Waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND.	35	2.34	82	24	1,968
§ 312.130; Requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24.	3	1	3	8	24
§§ 312.310(b) and 312.305(b); Submissions related to expanded access and treatment of an individual patient.	935	2.77	2,590	8	20,720
§ 312.310(d); Submissions related to emergency use of an investigational new drug.	480	2.15	1,032	16	16,512
§§ 312.315(c) and 312.305(b); Submissions related to expanded access and treatment of an intermediate-size patient population.	118	2.52	297	120	35,640
§ 312.320(b); Submissions related to a treatment IND or treatment protocol.	10	12.9	129	300	38,700

Table 1.--Estimated Annual Reporting Burden for Human Drugs (CDER)[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Total					23,125,527

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Recordkeeping Burden for Human Drugs (CDER)[1]

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
§ 312.52(a); Sponsor records for the transfer of obligations to a contract research organization.	1,300	1	1,300	2	2,600
§ 312.57; Sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug and any financial interests.	13,000	1	13,000	100	1,300,000
§ 312.62(a); Investigator recordkeeping of the disposition of drugs.	13,000	1	13,000	40	520,000
§ 312.62(b); Investigator recordkeeping of case histories of individuals.	13,000	1	13,000	40	520,000
§ 312.160(a)(3); Records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests.	547	1.43	782	0.50 (30 minutes)	391
§ 312.160(c); Shipper records of alternative disposition of unused drugs.	547	1.43	782	0.50 (30 minutes)	391
Total					2,343,382

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3.--Estimated Annual Third-Party Disclosure Burden for Human Drugs (CDER)[1]

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
§ 312.53(c); Investigator reports submitted to the sponsor, including Form FDA 1572, curriculum vitae, clinical protocol, and financial disclosure.	1,732	7.94	13,752	80	1,100,160
§ 312.55(a); Investigator brochures submitted by the sponsor to each investigator.	995	4	3,980	48	191,040
§ 312.55(b); Sponsor reports to investigators on new observations, especially adverse reactions and safe use.	995	4	3,980	48	191,040

Table 3.--Estimated Annual Third-Party Disclosure Burden for Human Drugs (CDER)[1]

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
§ 312.64; Investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports.	13,000	1	13,000	24	312,000
Total					1,794,240

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 4.--Estimated Annual Reporting Burden for Biologics (CBER)[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
312.2(e) Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.	217	1.18	256	24	6,144
312.8 Requests to charge for an investigational drug.	20	1.50	30	48	1,440
312.10 Requests to waive a requirement in part 312.	2	1	2	24	48
312.23(a) through (f) IND content and format.	335	1.35	452	1,600	723,200
312.30(a) through (e) Protocol amendments.	694	5.84	4,053	284	1,151,052
312.31 (b) Information amendments.	77	2.43	187	100	18,700
312.32(c) and (d) IND Safety reports.	161	8.83	1,422	32	45,504
312.33(a) through (f) IND Annual reports.	745	2.14	1,594	360	573,840
312.38(b) and (c) Notifications of withdrawal of an IND.	134	1.69	226	28	6,328
312.42 Sponsor requests that a clinical hold be removed, including sponsor submission of a complete response to the issues identified in the clinical hold order.	67	1.30	87	284	24,708
312.44(c) and (d) Sponsor responses to FDA when IND is terminated.	34	1.15	39	16	624
312.45(a) and (b) Sponsor requests for or responses to an inactive status determination of an IND by FDA.	55	1.38	76	12	912
312.47	88	1.75	154	160	24,640

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.					
312.53(c) Investigator reports submitted to the sponsor, including Form FDA-1572, curriculum vitae, clinical protocol, and financial disclosure.	453	6.33	2,867	80	229,360
312.54(a) Sponsor submissions to FDA concerning investigations involving an exception from informed consent under 21 CFR 50.24.	1	1	1	48	48
312.54(b) Sponsor notifications to FDA and others concerning an IRB determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in 50.24(a).	1	1	1	48	48
312.55(a) Number of investigator brochures submitted by the sponsor to each investigator.	239	1.91	456	48	21,888
312.55(b) Number of sponsor reports to investigators on new observations, especially adverse reactions and safe use.	243	4.95	1,203	48	57,744
312.56(b), (c), and (d) Sponsor notifications to FDA and others resulting from: (1) The sponsor's monitoring of all clinical investigations and determining that an investigator is not in compliance with the investigation agreements; (2) the sponsor's review and evaluation of the evidence relating to the safety and effectiveness of the investigational drug; and (3) the sponsor's determination that the investigational drug presents an unreasonable and significant risk to subjects.	108	2.21	239	80	19,120
312.58(a) Number of sponsor's submissions of clinical investigation records to FDA on request during FDA inspections.	7	1	7	8	56

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
312.64 Number of investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports.	2,728	3.82	10,421	24	250,104
312.70 During the disqualification process of a clinical investigator by FDA, the number of investigator responses or requests to FDA following FDA's notification to an investigator of its failure to comply with investigation requirements.	5	1	5	40	200
312.110(b)(4) and (b)(5) Number of written certifications and written statements submitted to FDA relating to the export of an investigational drug.	18	1	18	75	1,350
312.120(b) Number of submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND.	280	9.82	2,750	32	88,000
312.120(c) Number of waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND.	7	2.29	16	24	384
312.130 Number of requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24.	350	1.34	469	8	3,752
312.310(b) and 312.305(b) Number of submissions related to expanded access and treatment of an individual patient.	78	1.08	84	8	672
312.310(d) Number of submissions related to emergency use of an investigational new drug.	76	2.76	210	16	3,360
312.315(c) and 312.305(b) Number of submissions related to expanded access and treatment of an intermediate-size patient population.	9	1	9	120	1,080
312.320(b) Number of submissions related to a treatment IND or treatment protocol.	1	1	1	300	300
Total					3,254,606

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 5.--Estimated Annual Recordkeeping Burden for Biologics (CBER)[1]

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
312.52(a) Sponsor records for the transfer of obligations to a contract research organization.	75	1.40	105	2	210
312.57 Sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug, and any financial interests.	335	2.70	904	100	90,400
312.62(a) Investigator recordkeeping of the disposition of drugs.	453	1	453	40	18,120
312.62(b) Investigator recordkeeping of case histories of individuals.	453	1	453	40	18,120
312.160(a)(3) Records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests.	111	1.40	155	0.5 (30 minutes)	78
312.160(c) Shipper records of alternative disposition of unused drugs.	111	1.40	155	0.5 (30 minutes)	78
Total					127,006

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Because we have received an increased number of IND submissions since the last OMB approval of the information collection, we have increased our estimate of the associated burden accordingly.

Dated: September 28, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-21610 Filed: 10/3/2018 8:45 am; Publication Date: 10/4/2018]